REMARKS/ARGUMENT

Some typographical errors have been corrected in the specification.

The Examiner is thanked for numerous helpful suggestions and clarifications in the body of the Office Action. The present remarks are responsive to the issues and clarifications the Examiner has raised.

In particular, applicant appreciates that numerous objections under 35 U.S.C. §112 have been withdrawn. The only remaining § 112 objection relates to the term "androgenic agent" in claim 3, which the Examiner alleges to be overly broad and not supported by sufficient working examples. In response, applicant discusses herein the specific support for the term in the present specification and encloses a further explanation provided by prior art U.S. Patent 5,629,303.

An androgenic agent activates the androgen receptor. Because certain physiologic consequences flow from the activation of the receptor, it can be concluded that all compounds which activate the receptor should interchangeably provide that androgen-receptor mediated response. Many androgens are well known in the art, including such natural androgens as testosterone. Additionally, other preferred androgenic agents are discussed at page 22, lines 16-20 of the specification, where low dose progestins are recommended for providing the desired effect on the androgen receptor. Many such androgenic agents, such as these progestins, were already known in the art as evidence by applicant's own enclosed prior art U.S. Patent 5,629,303, where a large number of well-known androgenic compounds are listed at column 23, line 54 through column 24, line 33, including medroxyprogesterone acetate (MPA) and megestrol acetate, and many others.

The present specification provides a working example showing the favorable effects of the androgenic progestin MPA (on reducing cancer risk) in Figure. 4 (discussed in further detail at page 13, lines 11-17 of the present specification). The present specification also recommends these types of progestin for providing the claimed androgenic effect herein at page 22, lines 16-20.

In summary, the term "androgenic agent" is well known in the art. Many examples have been given and one specifically tested. The mechanism of action (through androgen receptor-mediated activity) assures interchangeability of various androgens for providing the desired androgen receptor-mediated effects.

Such recitations of a class of materials is proper under 35 U.S.C. §112, wherever the specification would lead one of skill in the art to expect and predict that specific members of the class will interchangeably provide the same function in the invention. In Re Hirschler, 591 F.2d 693, 701, 200 U.S.P.Q. 711 (C.C.P.A. 1979). The application at issue in Hirschler gave only a single example of a single steroid (dexamethasone 21-phosphate), in a claim that broadly recited all "steroids" as a class of materials whose penetration of human skin could be enhanced with DMSO. The Court of Customs and Patent Appeals noted:

> The question is simple: does the array of information supplied by appellant in the [relevant] application teach one having ordinary skill in this art that one of the class of steroids will operate in the claimed process. We conclude that it does.
>
> * * *
>
> Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids when considered as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar.

Hirschler, 591 F.2d at 701, 200 U.S.P.Q. at 717 (emphasis added).

Where the members of the generically recited class are expected to perform similarly in the invention, the dictates of §112 are met. There is no magic number of specific examples required. A single example was sufficient in Hirschler. Indeed, a specification without any examples can be sufficient in the appropriate case. See, e.g., In re Strahilevitz, 668 F.2d 1229, 1232, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982); In re Stephens, 529 F.2d 1343, 1345, 188 U.S.P.Q. 659, 661 (C.C.P.A. 1976); In re Borkowski, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970); In re Gay, 309 F.2d 769, 774, 135 U.S.P.Q. 311, 316 (C.C.P.A. 1962). All that

is required is a rational basis for expecting that the advantages of the invention will not be lost simply because one member of a generically recited class is chosen instead of another.

Because DMSO, as claimed in Hirschler, had provided a benefit (improved skin penetration) that was independent of the specific steroid selected, all steroids were expected to benefit, and all could be generically recited in the patent claim. Here, as in Hirschler, androgenic agents provide a benefit which all androgenic agents will enjoy, independent of which specific androgenic agent is chosen. Hence, the patent claims may generically recite "androgenic agents."

For all the foregoing reasons, it is urged that the Section 112 rejection of claim 3 should be withdrawn.

Claims 1, 3-6 and 13-28 stand rejected by the Examiner under 35 U.S.C. § 103 as allegedly obvious over Labrie '720, Labrie '201 and applicant's statement regarding the prior art in the specification at page 2, lines 3-4.

The cited references neither disclose nor suggest the presently-claimed combination which utilizes selective estrogen receptor modulators (SERMs) in the treatment of menopausal symptoms. The Examiner correctly notes that estrogens are known to be useful in the treatment of menopausal symptoms. However, the prior art would have expected diminished -- rather than improved -- results from addition of the compounds set forth in Labrie '201. The Examiner alleges that Labrie '201 suggests using its compounds for the presently-claimed treatment of menopausal symptoms. In fact, however Labrie '201 teaches away from using its compounds therein in connection with conditions (like menopause) that respond favorably to estrogen receptor activation. Labrie '201 is directed to preventing estrogen receptor activation, and the compounds therein are recommended only for use in connection with diseases which respond negatively to estrogen receptor activation. Menopause was known to respond positively. Labrie '201 expressly states that:

> "It is an object of the invention to provide compounds and compositions for reducing estrogen receptor activation . . . ."
> (Labrie '201, page 5, lines 2-3).

The Labrie '201 prior art also expressly states that its compounds are for use on diseases where estrogen receptor activation is a bad thing rather than a good thing, i.e., where the Labrie '201 compounds that suppress that activation would be useful:

> "It is another object of the invention to provide therapeutic compounds and compositions useful in the treatment of estrogen-related diseases (e.g., diseases whose onset or progress is aided by the activation of the estrogen receptor). These diseases include, but are not limited to breast cancer . . . ." (Labrie '201, page 5, lines 9-13).

Nothing in Labrie '201 remotely suggests use of the compounds therein on menopause or other conditions that improve when estrogen receptors are activated by estrogens. The Labrie '201 compounds would have been expected to suppress the very estrogen receptor activation that was known to aid in treatment of menopausal symptoms.

The Examiner's other contention that it would have been obvious to utilize the presently-claimed combination of estrogen and SERM for minimizing breast cancer risk is also contrary to the above-quoted teachings of the Labrie '201 prior art. The presently-claimed invention is a combination therapy which administers estrogen. However, the above-quoted language from the prior art specifically notes that breast cancer is a "disease whose onset or progress is aided by activation of the estrogen receptor." Estrogens, whose function is activation of the estrogen receptor, are strictly to be avoided according to that prior art teaching. Accordingly, it is urged that the rejection under 35 U.S.C. § 103 should be withdrawn.

Claim 2 stands rejected as allegedly obvious over the same prior art submitted against the other claims, and additionally, in view of Labrie '460. However, Labrie '460 does not cure the deficiencies of the other cited references, namely that none of the references -- alone or in combination -- teach the use of SERM in the treatment of menopause. The one reference that is relied upon for this purpose – as was the case in the above-discussed earlier Section 103 rejection -- is Labrie '201. However, as pointed out above, Labrie '201 recommends its compounds only for diseases which are made worse by activation of the estrogen receptor, an activation that Labrie '201 suppresses. Labrie '201 teaches away from the use of its compounds in situations where its suppression of estrogen receptor activation would not be believed

beneficial, e.g., regarding menopausal symptoms which react favorably to estrogen receptor activation. Accordingly, the further rejection of claim 2 under 35 U.S.C. § 103 should also be withdrawn.

It is believed that the application is now in condition for allowance. A Notice of Allowance is solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Asst. Commissioner for Patents, Washington, D.C. 20231, on March 20, 2003:

William O. Gray, III
Name of applicant, assignee or Registered Representative

Signature

March 20, 2003
Date of Signature

WOG:db

Respectfully submitted,

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APPENDIX A

"CLEAN" VERSION OF EACH PARAGRAPH/SECTION/CLAIM
37 C.F.R. § 1.121(b)(ii) AND (c)(i)

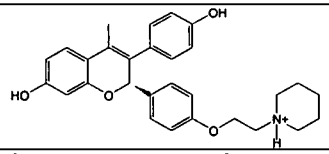
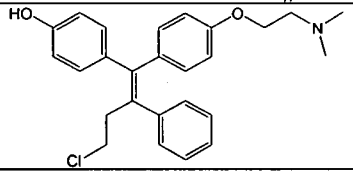
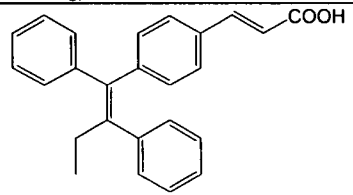
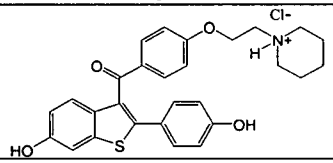
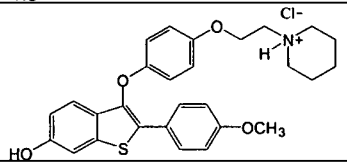
SPECIFICATION:

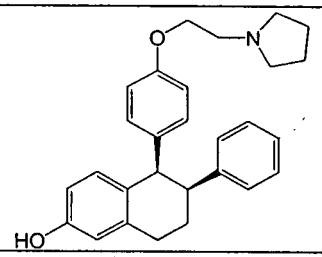
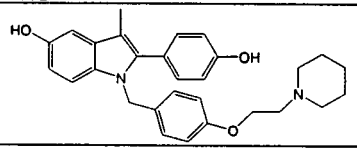
Replacement for the paragraph beginning at page 27, line 21 to page 28, line 4:

Estrogens are known to lower serum cholesterol but to increase or to have no effect on serum triglycerides levels (Love et al., Ann. Intern. Med. 115: 860-864, 1991; Walsh et al., New Engl. J. Med. 325: 1196-1204, 1991; Barrett-Connor, Am. J. Med. 95 (Suppl. 5A): 40S-43S, 1993; Russell et al., Atherosclerosis 100: 113-122, 1993; Black et al., J. Clin. Invest. 93: 63-69, 1994; Dipippo et al., Endocrinology 136: 1020-1033, 1995; Ke et al., Endocrinology 136: 2435-2441, 1995). Figures 1A and 1B show that EM-800 possesses both hypocholesterolemic and hypotriglyceridemic effects in the rat, thus showing its unique action on the serum lipid profile which is apparently different from other SERMs, such as tamoxifen (Bruning et al., Br. J. Cancer 58: 497-499, 1988; Love et al., J. Natl. Cancer Inst. 82: 1327-1332, 1990; Dipippo et al., Endocrinology 136: 1020-1033, 1995; Ke et al., Endocrinology 136: 2435-2441, 1995), droloxifene (Ke et al., Endocrinology 136: 2435-2441, 1995), and raloxifene (Black et al., J. Clin. Invest. 93: 63-69, 1994). Thus, it is believed that a combination of estrogen and EM-800 should preserved the hypocholesterolemic and hypotriglyceridemic effects of EM-800, thus suggesting that such a combination could exert beneficial effects on serum lipids.

Specification replacement for Table 8 , page 78, Row 2, Col. 3 as follows:

Table 8

NAME	CODE NAME	STRUCTURE	Maximal stimulation of alkaline phosphatase % of 1nM E_2 stimulation * (nb of experiments)	Inhibition of 1nM E_2-induced stimulation of alkaline phosphatase IC_{50} (nM) (nb of experiments)	Maximal inhibition of 1nM E_2-induced stimulation of alkaline phosphatase (nb of experiments)
EM-652.HCl	EM-652.HCl; (EM-1538)		1.88±0.26 (22)	1.52±0.22 (18)	98.97±0.174 (18)
OH-Toremifene	EM-880		29.6±2.1 (6)	72.1±7.6 (3)	75.73±3.52 (3)
GW-5638	EM-1796		7.75±5.5 (2)	No inhibition	
Raloxifene LY 156758	EM-1105		12.8±1.7 (8)	3.39±0.9 (6)	94.31±1.74 (5)
LY 353381	EM-1665		15.5±0.25 (5)	1.87±0.07 (2)	90.25±0.127 (2)

NAME	CODE NAME	STRUCTURE	Maximal stimulation of alkaline phosphatase	Inhibition of 1nM E_2-induced stimulation of alkaline phosphatase	Maximal inhibition of 1nM E_2-induced stimulation of alkaline phosphatase
Lasofoxifene (free base)	EM-3114		17.9 (1)	4.24 (1)	85.14 (1)
ERA-923	EM-3527		0.6 (1)	5.84 (1)	100.16 (1)

***% of 1nM E_2 stimulation =**
OD 405nm compound-OD 405nm basal/ OD 405nm 1nM E_2-OD 405nm basal
Please see also Labrie et al. EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium, J. Steroid Biochem. and Mol. Bio. 69, 51-84, 1999.

APPENDIX B
version with markings to show changes made
37 C.F.R. § 1.121(b)(iii) AND (c)(ii)

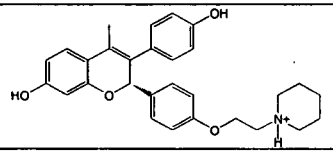
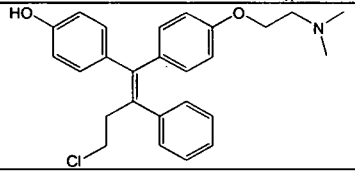
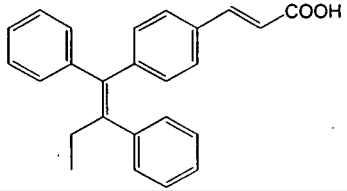
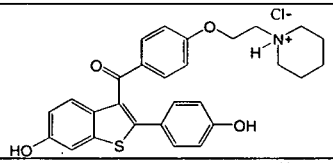
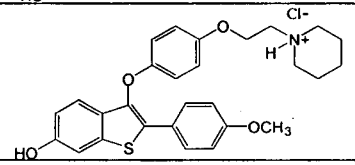
SPECIFICATION:

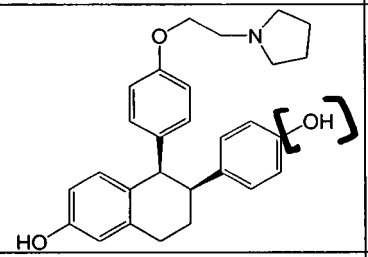
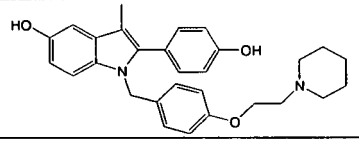
Paragraph at page 27, line 21 to page 28 line 4 :

Estrogens are known to lower serum cholesterol but to increase or to have no effect on serum triglycerides levels (Love et al., Ann. Intern. Med. 115: 860-864, 1991; Walsh et al., New Engl. J. Med. 325: 1196-1204, 1991; Barrett-Connor, Am. J. Med. 95 (Suppl. 5A): 40S-43S, 1993; Russell et al., Atherosclerosis 100: 113-122, 1993; Black et al., J. Clin. Invest. 93: 63-69, 1994; Dipippo et al., Endocrinology 136: 1020-1033, 1995; Ke et al., Endocrinology 136: 2435-2441, 1995). [Figure 3 shows] Figures 1A and 1B show that EM-800 possesses both hypocholesterolemic and hypotriglyceridemic effects in the rat, thus showing its unique action on the serum lipid profile which is apparently different from other SERMs, such as tamoxifen (Bruning et al., Br. J. Cancer 58: 497-499, 1988; Love et al., J. Natl. Cancer Inst. 82: 1327-1332, 1990; Dipippo et al., Endocrinology 136: 1020-1033, 1995; Ke et al., Endocrinology 136: 2435-2441, 1995), droloxifene (Ke et al., Endocrinology 136: 2435-2441, 1995), and raloxifene (Black et al., J. Clin. Invest. 93: 63-69, 1994). Thus, it is believed that a combination of estrogen and EM-800 should preserved the hypocholesterolemic and hypotriglyceridemic effects of EM-800, thus suggesting that such a combination could exert beneficial effects on serum lipids.

Attached are marked up page numbers 77-78 (page 78, Row 2, column 3), Table 8:

Table 8

NAME	CODE NAME	STRUCTURE	Maximal stimulation of alkaline phosphatase % of 1nM E_2 stimulation * (nb of experiments)	Inhibition of 1nM E_2-induced stimulation of alkaline phosphatase IC_{50} (nM) (nb of experiments)	Maximal inhibition of 1nM E_2-induced stimulation of alkaline phosphatase (nb of experiments)
EM-652.HCl	EM-652.HCl; (EM-1538)		1.88±0.26 (22)	1.52±0.22 (18)	98.97±0.174 (18)
OH-Toremifene	EM-880		29.6±2.1 (6)	72.1±7.6 (3)	75.73±3.52 (3)
GW-5638	EM-1796		7.75±5.5 (2)	No inhibition	
Raloxifene LY 156758	EM-1105		12.8±1.7 (8)	3.39±0.9 (6)	94.31±1.74 (5)
LY 353381	EM-1665		15.5±0.25 (5)	1.87±0.07 (2)	90.25±0.127 (2)

NAME	CODE NAME	STRUCTURE	Maximal stimulation of alkaline phosphatase	Inhibition of 1nM E_2-induced stimulation of alkaline phosphatase	Maximal inhibition of 1nM E_2-induced stimulation of alkaline phosphatase
Lasofoxifene (free base)	EM-3114		17.9 (1)	4.24 (1)	85.14 (1)
ERA-923	EM-3527		0.6 (1)	5.84 (1)	100.16 (1)

***% of 1nM E_2 stimulation =**

OD 405nm compound-OD 405nm basal/ OD 405nm 1nM E_2-OD 405nm basal
Please see also Labrie et al. EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium, J. Steroid Biochem. and Mol. Bio. 69, 51-84, 1999.